

## **IN THE CLAIMS:**

Please amend claim 8 and add new claim 13 as follows:

1. (Original) A method of measuring a structural change in a protein when the protein is contacted with a compound, comprising the steps of:
  - (a) selecting a domain in the protein;
  - (b) providing information on an orientation of the domain when the protein is not in contact with the compound;
  - (c) providing information on an orientation of the domain when the protein is in contact with the compound, by
    - (i) providing known atomic coordinates for the domain,
    - (ii) providing axial variations of NMR signals, which are generated from the protein in contact with the compound in the presence of a liquid crystalline material by two-dimensional TROSY NMR spectroscopy and depend on an orientation angle of the molecules in a magnetic field,
    - (iii) determining Saupe order matrix elements for the domain from the atomic coordinates for the domain and the axial variations of NMR signals, and
    - (iv) diagonalizing the determined matrix to produce the information on an orientation of the domain; and
  - (d) measuring the structural change in the protein by a difference between the information on an orientation provided in step (b) and the information on an orientation provided in step (c).
2. (Original) The method of measurement according to claim 1, wherein the step (b) is a step of:
  - (b) providing the information on an orientation of the domain when the protein is not in contact with the compound, by
    - (v) providing known atomic coordinates for the domain,
    - (vi) providing axial variations of NMR signals, which are generated from the protein in no contact with the compound in the presence of the liquid crystalline material by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the molecules in the magnetic field,
    - (vii) determining Saupe order matrix elements for the domain from the atomic

coordinates for the domain and the axial variations of NMR signals, and

(viii) diagonalizing the determined matrix to produce the information on an orientation of the domain.

3. (Original) The method of measurement according to claim 1, wherein the step (b) is a step of

(b) providing the information on an orientation of the domain from the atomic coordinates provided previously when the protein was not in contact with the compound.

4. (Original) The method of measurement according to claim 1, wherein in the step (c), the axial variations of NMR signals, which are generated by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the molecules in the magnetic field, are variations along a  $^{15}\text{N}$  axis.

5. (Original) The method of measurement according to claim 4, wherein the Saupe order matrix elements in (iii) are determined by:

with respect to the kth pair of  $^{15}\text{N}$  nuclear spins in the domain,

providing  $\phi_i^k$  as a vector angle of an N-H bond having the kth pair of spins in the domain to the ith molecular axis,

providing  $\phi_j^k$  as a vector angle of an N-H bond having the kth pair of spins in the domain to the jth molecular axis,

setting a static dipolar coupling  $D_{\text{nh}}^0$  at 23.0 kHz for a length of the N-H bond of 1.02 Å, or setting a static dipolar coupling  $D_{\text{nh}}^0$  at 21.7 kHz for a length of the N-H bond of 1.04 Å,

determining as  $\delta_{ij}$  a tensor value for chemical shift anisotropy of a  $^{15}\text{N}$  nucleus in an arbitrary residue of the protein, and

determining the Saupe order matrix elements  $S_{ij}$  defining the molecular orientation with respect to the magnetic field, by contacting the protein with the compound in the presence of the liquid crystalline material, providing  $\Delta\delta_{\text{troty}}(k)$  for the kth pair of  $^{15}\text{N}$  nuclear spins of the protein by two-dimensional TROSY NMR spectroscopy, and using the  $\Delta\delta_{\text{troty}}(k)$  together with the following equation (1):

$$\Delta\delta_{\text{troty}}(k) = \sum S_{ij} \{0.5 D_{\text{nh}}^0 \cos\phi_i^k \cos\phi_j^k + (2/3) \delta_{ij}\} \quad (1)$$

$i, j = x, y, z.$

6. (Original) The method of measurement according to claim 2, wherein in the step (b), the axial variations of NMR signals, which are generated by two-dimensional TROSY NMR spectroscopy and depend on the orientation angle of the molecules in the magnetic field, are variations along a  $^{15}\text{N}$  axis.

7. (Original) The method of measurement according to claim 6, wherein the Saupe order matrix elements in (vii) are determined by:

with respect to the  $k$ th pair of  $^{15}\text{N}$  nuclear spins in the domain,

providing  $\phi_i^k$  as a vector angle of an N-H bond having the  $k$ th pair of spins in the domain to the  $i$ th molecular axis,

providing  $\phi_j^k$  as a vector angle of an N-H bond having the  $k$ th pair of spins in the domain to the  $j$ th molecular axis,

setting a static dipolar coupling  $D_{\text{nh}}^0$  at 23.0 kHz for a length of the N-H bond of 1.02 Å, or setting a static dipolar coupling  $D_{\text{nh}}^0$  at 21.7 kHz for a length of the N-H bond of 1.04 Å,

determining as  $\delta_{ij}$  a tensor value for chemical shift anisotropy of a  $^{15}\text{N}$  nucleus in an arbitrary residue of the protein, and

determining the Saupe order matrix elements  $S_{ij}$  defining the molecular orientation with respect to the magnetic field, by making no contact of the protein with the compound in the presence of the liquid crystalline material, providing  $\Delta\delta_{\text{troty}}(k)$  for the  $k$ th pair of  $^{15}\text{N}$  nuclear spins by two-dimensional TROSY NMR spectroscopy, and using the  $\Delta\delta_{\text{troty}}(k)$  together with the following equation (1):

$$\Delta\delta_{\text{troty}}(k) = \sum S_{ij} \{0.5 D_{\text{nh}}^0 \cos\phi_i^k \cos\phi_j^k + (2/3) \delta_{ij}\} \quad (1)$$

$i, j = x, y, z.$

8. (Currently Amended) The method according to claim 5 [[or 7]], wherein a structural change in the protein when the protein and the compound are contacted is digitized as degree of orientational change by:

(ix) providing directions of orientation tensor axes by a first three unit vectors perpendicular to each other, by using the information on an orientation of the domain in the protein before the protein is contacted with the compound, wherein the first

three unit vectors are expressed by

$$\begin{array}{ccc} \longrightarrow & \longrightarrow & \longrightarrow \\ e_{fx}, & e_{fy}, & e_{fz} \end{array}$$

(x) providing directions of orientation tensor axes by a second three unit vectors perpendicular to each other, by using the information on an orientation of the domain in the protein after the protein is contacted with the compound, wherein the second three unit vectors are expressed by

$$\begin{array}{ccc} \longrightarrow & \longrightarrow & \longrightarrow \\ e_{bx}, & e_{by}, & e_{bz} \end{array}$$

(xi) denoting respective angles between the individual first unit vectors and the individual second unit vectors by a, b and c, and

(xii) giving a degree of orientational change by the following equation:  
degree of orientational change =  $a^2 + b^2 + c^2$ .

9. (Original) The method according to claim 2, further comprising a step of identifying a position on the protein to which the compound is bound.
10. (Original) The method according to claim 9, wherein the step of identifying a position on the protein to which the compound is bound is carried out by comparing the two-dimensional TROSY NMR spectrum obtained in the step (b) with the two-dimensional TROSY NMR spectrum obtained in the step (c) to detect a spectral change, and identifying an amino acid residue in the protein which has induced the spectral change.
11. (Original) The method according to claim 1, wherein the liquid crystalline material comprises a mixture selected from the group consisting of:
  - a mixture of dimyristoylphosphatidylcholine (DMPC) and dihexanoylphosphatidylcholine (DHPC),
  - a mixture of dimyristoylphosphatidylcholine (DMPC), dihexanoylphosphatidylcholine (DHPC), and sodium dodecyl sulfate (SDS),
  - a mixture of dimyristoylphosphatidylcholine (DMPC),

dihexanoylphosphatidylcholine (DHPC), and cetyltrimethylammonium bromide (CTAB),

a mixture of 1,2-di-O-dodecyl-sn-glycero-3-phosphocholine(DIODPC) and 3-(cholamidepropyl)-dimethylammonio-2-hydroxy-1-propane sulfate (CHAPS),

a mixture of n-alkyl-poly(ethyleneglycol)/n-alkylalcohol,

filamentous phage,

a mixture of cetylpyridinium chloride(CPCl)-hexanol-NaCl,

a mixture of cetylpyridinium bromide(CPBr)-hexanol-NaCl,

a purple membrane fragment of Halobacterium spp.,

microcrystalline cellulose, and

polyacrylamide gel.

12. (Original) The method according to claim 11, wherein the liquid crystalline material is the mixture of 7.5%(w/v) composed of dimyristoylphosphatidylcholine (DMPC), dihexanoylphosphatidylcholine (DHPC), and cetyltrimethylammonium bromide (CTAB)

13. (New) The method according to claim 7, wherein a structural change in the protein when the protein and the compound are contacted is digitized as degree of orientational change by:

(ix) providing directions of orientation tensor axes by a first three unit vectors perpendicular to each other, by using the information on an orientation of the domain in the protein before the protein is contacted with the compound, wherein the first three unit vectors are expressed by

$$\begin{array}{ccc} \longrightarrow & \longrightarrow & \longrightarrow \\ e_{fx}, & e_{fy}, & e_{fz} \end{array}$$

(x) providing directions of orientation tensor axes by a second three unit vectors perpendicular to each other, by using the information on an orientation of the domain in the protein after the protein is contacted with the compound, wherein the second three unit vectors are expressed by

$$\begin{array}{ccc} \longrightarrow & \longrightarrow & \longrightarrow \\ e_{bx}, & e_{by}, & e_{bz} \end{array}$$

(xi) denoting respective angles between the individual first unit vectors and the individual second unit vectors by  $a$ ,  $b$  and  $c$ , and

(xii) giving a degree of orientational change by the following equation:

$$\text{degree of orientational change} = a^2 + b^2 + c^2.$$